Cycloaromatization of Methyl (*E*)-4-(Methyllithio)-3-(1-pyrrolidinyl)-2-butenoate with α-Oxoketene *N,S*-Acetals: Direct Synthesis of 3,5-Bis(cycloalkylamino)biphenyls

Kethiri R. Reddy, Hiriyakkanavar Ila,* Hiriyakkanavar Junjappa*
Department of Chemistry, North-Eastern Hill University, Shillong – 793003, Meghalaya, India

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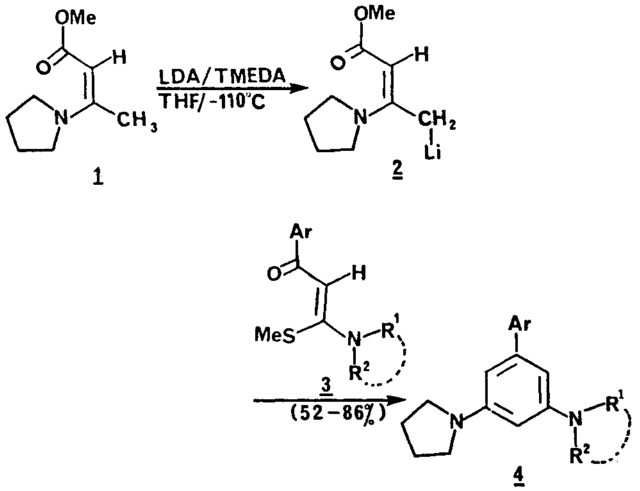
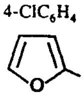
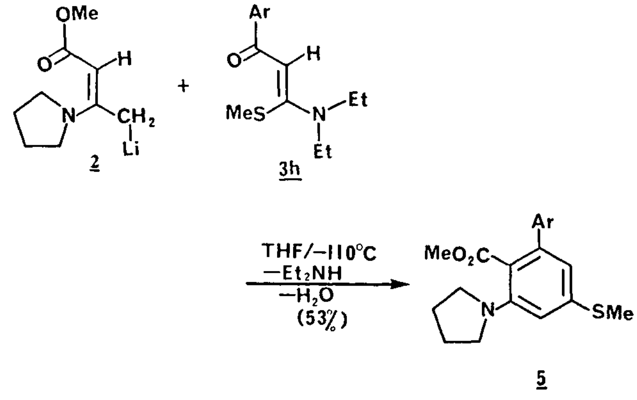
The vinyl carbanion **2** undergoes cycloaromatization with α-oxoketene *N,S*-acetals **3** through 1,4-conjugate addition–elimination process to afford 3,5-diaminobiphenyls **4** in good yields.

Enamines and 4-silylated 3-dialkylaminobutenoates are shown to undergo [4C + 2C] or [3C + 3C] annulation providing direct access to secondary and tertiary anilines.[1-3] However, these reactions are of limited synthetic utility for regiospecific introduction of the desired cycloalkylamino group in benzene ring. During the course of our studies on novel cycloaromatization reactions involving cyclocondensation of α-oxoketene dithioacetals (as a three carbon 1,3-electrophilic unit) with three carbon 1,3-binucleophiles,[4] we have recently reported the cyclization of these intermediates with methyl (*E*)-4-(methyllithio)-3-(1-pyrrolidinyl)-2-butenoate (**2**) to afford substituted and annulated anilines.[5] In continuation of these studies we have examined the reaction of **2** with α-oxoketene *N,S*-acetals **3**, with a view to synthesizing electron rich aromatic compounds carrying two cycloalkylamino groups. We report our successful results in this communication.

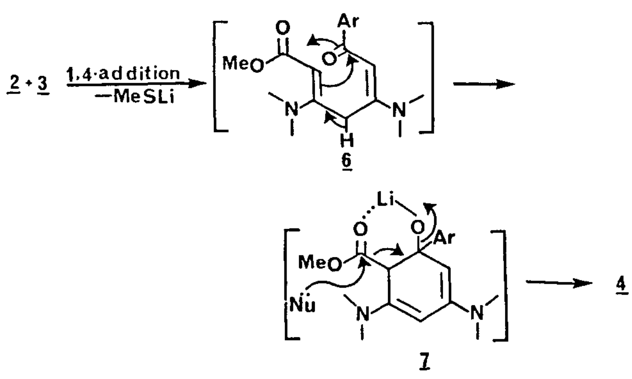


3.4	Ar	R¹	R²
a	C_6H_5	$-(CH_2)_4-$	
b	C_6H_5	$-(CH_2)_5-$	
c	$4-ClC_6H_4$	$-(CH_2)_5-$	
d	$4-ClC_6H_4$	$-(CH_2)_2-O-(CH_2)_2-$	
e	C_6H_5	$-(CH_2)_2-O-(CH_2)_2-$	
f	$4-ClC_6H_4$	$-(CH_2)_2-O-(CH_2)_2-$	
g		$-(CH_2)_2-O-(CH_2)_2-$	

The vinyl carbanion **2** was generated by deprotonation of methyl (*E*)-3-(1-pyrrolidinyl)-2-butenoate (**1**) with lithium diisopropylamide (LDA).[5] Treatment of **2** with *N,S*-acetal **3a** followed by subsequent workup yielded directly the bis(dialkylamino)biphenyl **4a** in 73 % yield. Other *N,S*-acetals **3b–g** also reacted with **2** in similar manner to afford **4b–g** in 52–86 % overall yields. However, the corresponding diethylamino *N,S*-acetal **3h** yielded the carboxylate **5** instead of the expected diethylaminobiphenyl under these conditions.



The reaction provides a facile entry to a regiospecifically substituted hitherto unknown class of electron rich bis(cycloalkylamino)biphenyls[9,10] as potential electron donors and bases. The proposed mechanism for the cyclization involves γ-1,4-conjugate addition of **2** to *N,S*-acetals[6-8] to give the intermediate **6** which undergoes spontaneous cyclization and decarbomethoxylation under the reaction conditions to afford **4** exclusively. In the addition of **2** to *N,S*-acetal **3h**, diethylamino group is eliminated instead of the methylthio group, thus affording **5**.



Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. IR spectra were obtained on a Perkin-Elmer 297 and Perkin-Elmer 983 spectrometers. ^1H NMR (90 MHz) spectra were recorded on Varian EM-390 spectrometer. Mass spectrum measurements were carried out with Jeol JMS D-300 mass spectrometer. Elemental analyses were performed on a Heraeus CHN-O-Rapid elemental Analyzer.

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Table 3,5-Bis(cycloalkylamino)biphenyls **4a–g**, and Methyl (4-Methylthio-6-phenyl-2-(1-pyrrolidinyl)benzoate (**5**)

Product[a]	Yield[b] (%)	mp (°C)	IR(KBr) (cm^{-1})	^{1}H NMR (CDCl$_3$/TMS) δ, J (Hz)	MS (70 eV) m/z (%)
4a	73	173–174	2827, 1592, 1570, 1354, 1177	1.80–2.20 (m, 8H, CH$_2$), 3.26–3.56 (m, 8H), NCH$_2$), 5.90 (br s, 1H$_{\text{arom}}$), 6.30 (br s, 2H$_{\text{arom}}$), 7.63–7.86 (m, 5H$_{\text{arom}}$)	292 (M$^+$, 100)
4b	86	128–130	2950, 1610, 1230, 760	1.53–2.13 (m, 10H, CH$_2$), 3.30–3.50 (m, 8H, NCH$_2$), 6.40 (br s, 2H$_{\text{arom}}$), 6.63 (br s, 1H$_{\text{arom}}$), 7.36–7.73 (m, 5H$_{\text{arom}}$)	306 (M$^+$, 65.9)
4c	68	152–153	3420, 2940, 1600, 1450, 1220, 1100	1.50–1.80 (m, 6H, CH$_2$), 1.86–2.10 (m, 4H, CH$_2$), 3.03–3.43 (m, 8H, NCH$_2$), 5.97 (br s, 1H$_{\text{arom}}$), 6.10 (br s, 1H$_{\text{arom}}$), 6.32 (br s, 1H$_{\text{arom}}$), 7.26–7.56 (m, 4H$_{\text{arom}}$)	340 (M$^+$, 100), 342 (20)
4d	78	122–124	2800, 2750, 1600, 1460, 1250	1.30–1.70 (m, 6H, CH$_2$), 1.70–2.00 (m, 4H, CH$_2$), 2.96–3.36 (m, 8H, NCH$_2$), 3.72 (s, 3H, OCH$_3$), 6.06 (br s, 1H$_{\text{arom}}$), 6.21 (brs, 1H$_{\text{arom}}$), 6.42 (br s, 1H$_{\text{arom}}$), 6.87 (d, 2H$_{\text{arom}}$, $J = 9$), 7.47 (d, 2H$_{\text{arom}}$, $J = 9$)	336 (M$^+$, 100)
4e	66	148–149	3457, 2960, 1593, 430	1.83–2.10 (m, 4H, CH$_2$), 3.10–3.46 (m, 4H, NCH$_2$), 3.73–3.93 (m, 4H, OCH$_2$), 3.73–3.93 (m, 4H, OCH$_2$), 6.14 (br s, 1H$_{\text{arom}}$), 6.40 (br s, 1H$_{\text{arom}}$), 6.53 (br s, 1H$_{\text{arom}}$), 7.33–7.76 (m, 5H$_{\text{arom}}$)	308 (M$^+$, 100)
4f	52	151–153	3329, 2822, 1581, 1214, 1117	1.90–2.20 (m, 4H, CH$_2$), 3.13–3.56 (m, 8H, NCH$_2$), 3.80–4.03 (m, 4H, OCH$_2$), 6.18 (br s, 1H$_{\text{arom}}$), 6.30 (br s, 1H$_{\text{arom}}$), 6.50 (br s, 1H$_{\text{arom}}$), 7.36–7.73 (m, 4H$_{\text{arom}}$)	358 (M$^+$, 100)
4g	68	68–70	1610, 1580, 1460, 1230, 1122, 1020	1.89–2.19 (m, 4H, CH$_2$), 3.13–3.59 (m, 8H, NCH$_2$), 3.84–4.14 (m, 4H, OCH$_2$), 6.27 (br s, 1H$_{\text{arom}}$), 6.63–6.83 (m, 2H, 3′-furyl, 1H$_{\text{arom}}$), 6.83–6.99 (m, 2H, 4′-furyl, 1H$_{\text{arom}}$), 7.77 (br s, 1H, 5′-furyl)	298 (M$^+$, 100)
5	53	73–74	3450, 1714 (C=O), 1410, 1248, 1075	1.93 (m, 4H, CH$_2$), 2.26 (s, 3H, SCH$_3$), 3.25 (t, 4H, NCH$_2$, $J = 9.3$), 3.84 (s, 3H, OCH$_3$), 6.68 (d, 2H$_{\text{arom}}$, $J = 3.1$), 7.25–7.37 (m, 3H$_{\text{arom}}$), 7.50 (d, 2H$_{\text{arom}}$, $J = 9.3$)	295 (M$^+$ − 32, 100), 280 (75), 235 (73)

[a] Satisfactory microanalyses obtained: C ± 0.32, H ± 0.31, N ± 0.30.

[b] Yield of pure, isolated product.

3,5-Bis(cycloalkylamino)biphenyls 4; General Procedure:

To an ice cooled (0 °C) solution of *i*-Pr$_2$NH (1.5 mL, 10 mmol) in anhydr. THF (10 mL) under dry Ar, was added 1 M solution of BuLi in Et$_2$O (7.5 mL, 10 mmol). To the resulting solution of LDA under dry Ar at −110 °C, was added *N,N,N′,N′*-tetramethylethylenediamine (TMEDA, 1.5 mL, 10 mmol) followed by a solution of the ester **1** (0.84 g, 5 mmol) in anhydr. THF (25 mL). The mixture was stirred at −110 °C for 30–45 min and at r.t. for 1 h. After cooling to −110 °C, a solution of α-oxoketene *N,S*-acetal **3** (5 mmol) in anhydr. THF (20 mL) was added followed by further stirring at r.t. for 5–6 h (monitored by TLC). The mixture was quenched with sat aq NH$_4$Cl (100 mL) extracted with CHCl$_3$ (3 x 25 mL) and the combined extracts were evaporated to give a viscous residue which was purified by column chromatography over silica gel using hexane/EtOAc (98:2) as eluent.

In the case of *N,S*-acetal **3h** the corresponding benzoate **5** was obtained under identical conditions (Table).

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